ORIGINAL ARTICLE

Pancreaticobiliary Anomalies is the Leading Cause of Childhood Recurrent Pancreatitis

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Background/Purpose: To explore the etiology, age and gender distribution, complications, and prognosis of recurrent pediatric pancreatitis.

Methods: Between 1993 and 2005, 92 children were hospitalized at the National Taiwan University Hospital with pancreatitis. Only 25 diagnosed with recurrent pancreatitis, based on two or more episodes of pancreatitis, elevated serum amylase and/or lipase levels ≥3 times the upper limit of normal, radiographic evidence, and clinical symptoms, were enrolled.

Results: A total of 85 episodes of pancreatitis in 25 patients (16 girls, 9 boys; mean age, 9.5±4.4 years; 3.4±1.9 episodes per person) were documented. The recurrence rate of pediatric pancreatitis was 27.2%. Recurrent pancreatitis was associated with pancreaticobiliary structural anomalies ($n=7$), biliary stones or sludge ($n=4$), hyperlipidemia ($n=3$), pseudopapillary tumor of the pancreas ($n=2$), trauma ($n=2$), hypoxic encephalopathy with recurrent bacteremia and sepsis ($n=1$), and idiopathic ($n=6$). The age and gender distribution according to etiologies were not different ($p=0.301$ for age, $p=0.137$ for gender). Complications included cholangitis or cholestasis (16%), pancreatic necrosis (16%), pseudocyst formation (12%), shock (8%), hemorrhagic pancreatitis (4%), and diabetes mellitus (4%). No patient died of recurrent pancreatitis. Long-term morbidity after recurrent pancreatitis presented as gout, diabetes mellitus, non-alcoholic steatohepatitis, and chronic pancreatitis.

Conclusion: For children who suffer from recurrent pancreatitis, pancreaticobiliary structural anomalies should be considered first. [*J Formos Med Assoc* 2007;106(2):119–125]

Key Words: children, pancreatitis, recurrent

Pancreatitis in children is relatively unusual and the etiologies are quite different between children and adults.[1–3] Although much has been reported on the etiologies, clinical presentations, diagnostic evaluation, and prognosis of acute pancreatitis in children, we are interested in recurrent pancreatitis, which is seen in about 10% of children with acute pancreatitis.[1,4]

The reported etiologies of recurrent pancreatitis include pancreaticobiliary structural anomalies, gallbladder stones or sludge, dysfunction of the sphincter of Oddi, familial or hereditary pancreatitis, autoimmune pancreatitis, hyperlipidemia or other metabolic causes (e.g. hypercalcemia), and idiopathic.[2,5] This study aimed to: (1) examine the etiology, age and gender distribution, prognosis,

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Received: January 17, 2006
Revised: February 24, 2006
Accepted: July 4, 2006

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and complications of recurrent pancreatitis in Taiwanese children, and (2) develop an algorithm for the work-up of such cases.

Methods

Between January 1, 1993 and June 30, 2005, 92 children < 18 years of age were hospitalized at the National Taiwan University Hospital with pancreatitis. Only 25 diagnosed with recurrent pancreatitis were enrolled. The following data were analyzed: age at onset of the first episode of pancreatitis, gender, episodes of pancreatitis, etiology, comorbidity, associated family histories, laboratory results of peak serum amylase, peak lipase, lipid profiles, and bilirubin levels. Imaging studies from sonography, endoscopic, and radiologic examinations and surgical procedures were recorded.

The classification of pancreatitis includes acute and chronic pancreatitis. Acute pancreatitis was diagnosed by serum amylase and/or lipase levels ≥ 3 times the upper limit of normal, radiographic evidence, and clinical symptoms of pancreatitis according to the Atlanta Classification.[6] There were no cases of pseudopancreatitis in this series. Irreversible changes in the architecture and function of the pancreas were considered as chronic pancreatitis.[7] Imaging findings of chronic pancreatitis demonstrated long-standing pancreatic injury such as intraductal calcification, parenchymal atrophy, or main pancreatic duct dilatation.[8,9] In our study, "recurrent pancreatitis" was defined as two or more episodes of pancreatitis with 2-week symptom-free intervals. These patients might turn out to be diagnosed with chronic pancreatitis later in their clinical courses.[10]

Ultrasonography (US) was the primary screening tool for pancreatic evaluation.[11] Computed tomography (CT) was performed to evaluate pancreatitis and its complications, pancreatic trauma, and neoplastic conditions. Magnetic resonance imaging (MRI), in combination with magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic retrograde cholangiopancreatography (ERCP), were indicated when children were suspected of pancreaticobiliary structural anomalies.

The presence of anomalous pancreaticobiliary junction (APBJ) was defined as a long common channel located outside the duodenal wall ≥ 7 mm as shown by MRCP or ERCP.[12,13] We excluded iatrogenic acute pancreatitis induced by the ERCP procedure. Idiopathic pancreatitis was considered only when a patient had no known etiologies after extensive history taking and laboratory and image examinations.

Statistical analysis was performed using the Kruskal-Wallis and χ^2 tests as appropriate.

Results

In the past 12 years, 25 Taiwanese children were diagnosed with recurrent pancreatitis at the Department of Pediatrics, National Taiwan University Hospital. The recurrence rate of pediatric pancreatitis was 27.2%. There were 85 episodes of pancreatitis occurring in 25 patients (3.4 ± 1.9 episodes per person), of whom 16 (64%) were girls. Six (24%) were considered to have chronic pancreatitis while 19 (76%) were diagnosed with recurrent acute pancreatitis.

The etiologies, episodes, age at onset of the first episode of pancreatitis, and gender information of patients with recurrent pancreatitis are listed in Table 1. These patients were divided into three groups for statistical analysis: pancreaticobiliary diseases ($n = 11$), idiopathic ($n = 6$), and other etiologies ($n = 8$). The age at onset of the first episode of pancreatitis and gender distribution of pediatric recurrent pancreatitis were not different by statistical analysis ($p = 0.301$ for age, Kruskal-Wallis test; $p = 0.137$ for gender, χ^2 test).

The clinical symptoms and signs, laboratory data, and imaging tools for the diagnosis of pediatric recurrent pancreatitis are summarized in Tables 2 and 3. Surgical interventions and prior surgical histories before the pancreatitis attack are listed in Table 4. The imaging findings of pancreatitis using different tools are listed in Table 5.

Table 1. Etiology, age and gender information of the 25 pediatric patients with recurrent pancreatitis

Etiology	*n* (%)	Episodes, *n* (range)	Age (yr) at onset*	F:M
Structural anomalies†	7 (28)	3 (2–4)	7.7 (1.0–12.7)	6:1
GB stones or sludge	4 (16)	3 (2–6)	12.6 (4.5–13.5)	3:1
Hyperlipidemia	3 (12)	2 (2–3)	15.9 (8.5–17.1)	1:2
Pancreatic tumor	2 (8)	2.5 (2–3)	14.0, 15.2	1:1
Physical trauma	2 (8)	4 (2–6)	7.2, 10.0	1:1
Sepsis	1 (4)	2	4.1	0:1
Idiopathic	6 (24)	4.5 (2–9)	8.8 (4.8–15.2)	4:2
Total	25 (100)	85	9.5 ± 4.4	16:9

**Age at onset is the age at the first pancreatitis attack and is presented as median and range of minimum and maximum values; †structural anomalies included pancreaticobiliary structural anomalies and extrapancreatic abnormalities, e.g. duodenal atresia. GB = gallbladder; F:M = female to male ratio.*

Table 2. Clinical symptoms and signs and family histories of the 25 pediatric patients with recurrent pancreatitis

Signs/symptoms	*n* (%)
Abdominal pain	24 (96)
Nausea/vomiting	17 (68)
Fever	6 (24)
Jaundice	4 (16)
Diarrhea	3 (12)
Hypotension	2 (8)
Family histories*	2 (8)
Peritonitis	1 (4)

**Family histories related to pancreatitis included family members with pancreatitis, hyperlipidemia, and autoimmune disease. In the two cases, family histories were hyperlipidemia in a patient with gallstone, and acute pancreatitis and systemic lupus erythematosus in a patient with traumatic pancreatitis.*

Table 3. Laboratory, imaging, and pathologic findings in the 25 pediatric patients with recurrent pancreatitis

Findings	*n* (%)
Amylase > 390 U/L	15/25 (60)
Lipase > 130 U/L	22/24 (91.7)
Imaging tools	
Abnormal US	19/22 (86.4)
Abnormal CT	15/15 (100)
Abnormal MRI/MRCP	16/18 (88.9)
Abnormal ERCP	7/9 (77.8)
Abnormal pathology*	2/2 (100)

**Abnormal pathology consisted of solid and papillary epithelial neoplasms of the pancreas. US = ultrasonography; CT = computed tomography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; ERCP = endoscopic retrograde cholangiopancreatography.*

Eleven (44%) children with pancreatitis were found to have underlying pancreaticobiliary diseases, including pancreaticobiliary structural anomalies ($n=7$) and biliary stones or sludge ($n=4$). Pancreaticobiliary structural anomalies implied anatomic or developmental abnormalities of the biliary tract, pancreas, or duodenum. Seven cases were diagnosed with choledochal cyst ($n=4$), annular pancreas ($n=2$), and duodenal atresia ($n=1$). Among the four patients with choledochal cyst, two had an associated anomaly of APBJ. In the two cases with annular pancreas, one had an associated anomaly of APBJ and the other had pancreatic divisum. In the case of duodenal atresia, pancreatic divisum was also diagnosed. Pancreatic divisum was also found in one case with biliary sludge.

In cases with hyperlipidemia, triglyceride was > 1000 mg/dL at the diagnosis of pancreatitis. None of the three had a positive family history. One case was complicated with gout, another with pancreatic insufficiency, diabetes mellitus, and nonalcoholic steatohepatitis, and the third was lost to follow-up. Two cases with pancreatic tumor presented with chronic intermittent abdominal pain and abdominal mass on imaging examinations. Surgery was performed for tumor resection of the pancreatic head in one case and of the pancreatic

Table 4. Surgical management and prior surgical histories of the 12 pediatric cases with recurrent pancreatitis

	Diseases (*n*)
Surgical intervention	
Cholecystectomy	Gallstone (1)
	Idiopathic pancreatitis (1)
Choledochojejunostomy	Choledochal cyst (1)
Endoscopic internal drainage	Pseudocyst formation (1)
Pancreaticojejunostomy	Chronic pancreatitis (1)
Pancreatic ductogastrostomy	Chronic pancreatitis (1)
Prior operation before pancreatitis	
Duodenojejunostomy	Annular pancreas (1)
	Duodenal atresia (1)
Duodenoduodenostomy	Annular pancreas (1)
Choledochojejunostomy	Choledochal cyst (1)
Resection of pancreatic tumor	Pseudopapillary tumor of the pancreas (2)

Table 5. Imaging results of the pancreas using different tools in children with recurrent pancreatitis

	n (%)	Diagnostic tools
Pancreas edema	12/25 (48)	US, CT or MRI/MRCP
Pancreatic duct dilatation	12/25 (48)	US, CT, MRI/MRCP or ERCP
Peripancreatic changes	7/25 (28)	US, CT or MRI/MRCP
APBJ	5/25 (20)	MRI/MRCP and/or CT
Pancreatic necrosis	4/25 (16)	US, CT or MRI/MRCP
Ascites	4/25 (16)	US, CT or MRI/MRCP
Pseudocyst or abscess	3/25 (12)	US or CT
Pancreatic divisum	3/25 (12)	MRI/MRCP
Pancreatic tumor	2/25 (8)	US, CT, MRI/MRCP or ERCP
Irregular pancreatic duct	1/25 (4)	US, CT or MRI/MRCP

US = ultrasonography; CT = computed tomography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; ERCP = endoscopic retrograde cholangiopancreatography; APBJ = anomalous pancreaticobiliary junction.

tail in the other. Both were diagnosed with pseudopapillary epithelial tumor by histologic examinations and complicated with chronic pancreatitis.

One patient who had hypoxic ischemic encephalopathy also had recurrent pneumonia with sepsis. There were two episodes of sepsis-related severe pancreatitis, which became chronic pancreatitis. In patients with trauma-related recurrent pancreatitis ($n=2$), one had a complication with pseudocyst and underwent endoscopic internal drainage. The other progressed to chronic pancreatitis. Among the six cases (24%) of idiopathic pancreatitis, only one became chronic pancreatitis with chronic abdominal pain despite pancreatic ductojejunostomy.

Long-term morbidity after recurrent pancreatitis presented as chronic pancreatitis ($n=6$), gout ($n=2$), diabetes mellitus ($n=1$), and nonalcoholic steatohepatitis ($n=1$) in the 21 follow-up cases. Local and systemic complications of recurrent pancreatitis included cholangitis or cholestasis ($n=4$, 16%), pancreatic necrosis ($n=4$, 16%), pseudocyst formation ($n=3$, 12%), shock ($n=2$, 8%), hemorrhagic pancreatitis ($n=1$, 4%), and diabetes mellitus ($n=1$, 4%). No patient died of recurrent pancreatitis in this series,

although one patient died of pneumonia during follow-up.

Discussion

Biliary disease is one of the most common causes of acute pancreatitis in adults.[12] In children who suffer from recurrent pancreatitis, pancreaticobiliary structural anomalies should be considered first. Serum lipase elevations and CT examination are sensitive for the diagnosis and evaluation of the extent and complication of pancreatitis (Table 3).

Pancreatitis associated with anatomic or developmental abnormalities of the biliary tract, pancreas, or duodenum are diagnosed by imaging studies. US is the primary tool and CT is the best modality for evaluating pancreatitis and its complications.[11,14] In patients suspected of anatomic or developmental abnormalities of the biliary tract, pancreas, or duodenum, MRI/MRCP is a powerful tool for imaging of the pancreatic duct and biliary system, especially in pediatric cases.[11,14] On the other hand, because ERCP requires radiologic support, its use in children is limited.[15] A normal MRCP may obviate the need for ERCP.[11] These imply the importance of more than one imaging examination in pediatric recurrent pancreatitis.

APBJ is often associated with biliary tract and pancreatic diseases, e.g. choledochal cyst, bile duct and gallbladder carcinoma, and recurrent pancreatitis.[13,16] In our cases of annular pancreas, the associated structural anomalies of APBJ or pancreatic divisum were considered the most possible causes of recurrent bouts of pancreatitis. Although pancreatic divisum may be a normal variant and present in about 10% of the population, this anomaly should be carefully evaluated by MRCP or ERCP in children with recurrent pancreatitis without any other cause.[17]

The recurrence rate of pediatric pancreatitis was higher in our study, especially in patients with idiopathic pancreatitis. In the reports of Werlin et al[1] and Benifla and Weizman,[4] the incidences of recurrent pediatric pancreatitis were 12.2% and 9%, respectively. The discrepancy may be due to the stricter diagnostic criteria of acute pancreatitis in our study. The higher rate of recurrence is associated with the decreased number of cases diagnosed with acute pancreatitis compared to other groups. Evaluation and therapy in these cases is important because untreated patients experience recurrent episodes that may lead to chronic pancreatitis.[18] The benefit of sphincterotomy may provide reduction in the frequency of recurrent acute pancreatitis and relieve the pressure of pancreaticobiliary junction.[12,19] In our cases who were suspected of having gallbladder sludge or sphincter of Oddi dysfunction, they did not receive sphincterotomy for no absolute indications and instrumental limitations.

Surgical management is also important for underlying pancreaticobiliary structural anomalies, gallstones, and biliary sludge. Hepatojejunostomy for choledochal cyst is beneficial for the prevention of liver injury, biliary sludge, stone formation, and pancreatitis.[20] When gallbladder sludge is associated with biliary pain or recurrent attacks of acute pancreatitis, it is suggested that cholecystectomy should be done for gallstone pancreatitis.[21] Early surgical drainage of dilated ducts to relieve obstructed pancreatic flow is necessary to preserve exocrine and endocrine function and to relieve recurrent pain.[22]

Past surgical histories may suggest possible underlying diseases associated with pancreatitis. For example, patients with annular pancreas or duodenal atresia undergo duodenoduodenostomy or duodenojejunostomy in the neonatal period. The possible presence of APBJ or pancreatic divisum is not known until recurrent pancreatitis occurs years later. In another point of view, pancreatic tumor is not the true etiology of pancreatitis. However, the mass lesion may obstruct the pancreatic duct and cause recurrent pancreatitis. Resection of the pancreatic tumor might also cause pancreatic injury. In our study, one patient who had pseudopapillary tumor of the pancreas had three episodes of pancreatitis within 4 months after tumor resection. The other had several attacks of pancreatitis before a diagnosis of pancreatic neoplasm was made and had one episode of pancreatitis 3 years after resection.

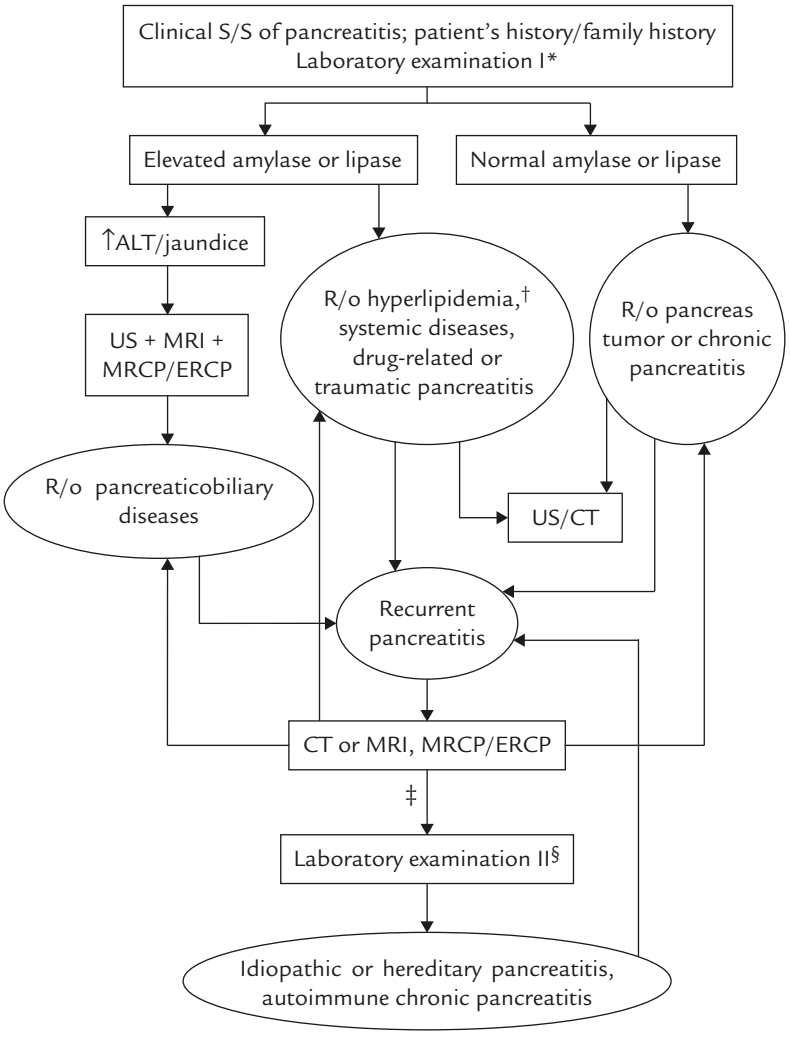

Figure. Proposed algorithm for the diagnosis of (recurrent) pancreatitis in children. The oval boxes represent possible diagnoses while the square boxes represent the laboratory and imaging examinations that need to be performed. S/S = symptoms/signs. *Laboratory examination I consists of serum amylase, lipase, bilirubin total/direct, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, triglyceride, cholesterol, C-reactive protein, sugar, blood culture, viral studies, and stool trypsin test (which was performed in cases of recurrent pancreatitis or failure to thrive). †In cases of hyperlipidemia-related pancreatitis, the lipid profiles in patients and other family members should be evaluated. ‡If no diagnosis is established after the above studies, consider Laboratory examination II. §Laboratory examination II consists of antinuclear antibodies, antimitochondrial antibodies, total immunoglobulin G, sweat test, and genetic study of cystic fibrosis transmembrane conductance regulator gene, serine protease inhibitor (kazal-type 1 genes), and protease serine 1 (cationic trypsinogen gene) if indicated. US = ultrasonography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; ERCP = endoscopic retrograde cholangiopancreatography; CT = computed tomography.

In conclusion, the major cause of recurrent pancreatitis in children is pancreaticobiliary disease. An algorithm is proposed by which the diagnosis of recurrent pediatric pancreatitis may be made (Figure). Structural anomalies can be treated by surgical correction, while underlying diseases of hyperlipidemia and metabolic abnormalities can be diagnosed and treated early. Careful follow-up is essential.

References

1. Werlin SL, Kugathasan S, Frautschy BC. Pancreatitis in children. *J Pediatr Gastroenterol Nutr* 2003;37:591–5.
2. Yeung CY, Lee HC, Hung FY, et al. Pancreatitis in children—experience with 43 cases. *Eur J Pediatr* 1996; 155:458–69.
3. Tiao MM, Chuang JH, Ko SF, et al. Pancreatitis in children: clinical analysis of 61 cases in Southern Taiwan. *Chang Gung Med J* 2002;25:162–8.

4. Benifla M, Weizman Z. Acute pancreatitis in childhood: analysis of literature data. *J Clin Gastroenterol* 2003;37: 169–72.
5. Whitcomb DC, Lowe ME. Pancreatitis. In: Walker WA eds. *Pediatric Gastrointestinal Disease*, 4th edition. Hamilton: BC Decker Inc, 2004:1586–8.
6. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11 through 13, 1992. *Arch Surg* 1993;128:586–90.
7. Lowe ME. Pancreatitis in childhood. *Curr Gastroenterol Rep* 2004;6:240–6.
8. Remer EM, Baker ME. Imaging of chronic pancreatitis. *Radiol Clin North Am* 2002;40:1229–42.
9. Ahmed SA, Wray C, Rilo HL, et al. Chronic pancreatitis: recent advances and ongoing challenges. *Curr Probl Surg* 2006;43:135–238.
10. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001;120:682–707.
11. Nijs E, Callahan MJ, Taylor GA. Disorders of the pediatric pancreas: image features. *Pediatr Radiol* 2005;35: 368–73.
12. Choi BH, Lim YJ, Yoon CH, et al. Acute pancreatitis associated with biliary disease in children. *J Gastroenterol Hepatol* 2003;18:915–21.
13. Guelrud M, Morera C, Rodriguez M, et al. Sphincter of Oddi dysfunction in children with recurrent pancreatitis and anomalous pancreaticobiliary union: an etiology concept. *Gastrointest Endosc* 1999;50:194–9.
14. Vaughn DD, Jabra AA, Fishman EK. Pancreatic disease in children and young adults: evaluation with CT. *Radiographics* 1998;18:1171–87.
15. Brown CW, Werlin SL, Geenen JE, et al. The diagnostic and therapeutic role of endoscopic retrograde cholangiopancreatography in children. *J Pediatr Gastroenterol Nutr* 1993;17:19–23.
16. Yu ZL, Zhang LJ, Fu JZ, et al. Anomalous pancreaticobiliary junction: image analysis and treatment principles. *Hepatobiliary Pancreat Dis Int* 2004;3:136–9.
17. Wanger CW, Golladay ES. Pancreas divisum and pancreatitis in children. *Am Surg* 1988;54:22–6.
18. Venu RP, Geenen JE, Hogan W, et al. Idiopathic recurrent pancreatitis: an approach to diagnosis and treatment. *Dig Dis Sci* 1989;34:56–60.
19. Bank S, Indaram A. Causes of acute and recurrent pancreatitis: clinical considerations and clues to diagnosis. *Gastroenterol Clin North Am* 1999;28:571–87.
20. Lai HS, Duh YC, Chen WJ, et al. Manifestation and surgical treatment of choledochal cyst in different age group patients. *J Formos Med Assoc* 1997;96:242–6.
21. Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. *New Engl J Med* 1992;326:589–93.
22. Lin YT, Chang MH, Hsu HY, et al. A follow-up study of annular pancreas in infants and children. *Acta Paed Sin* 1998;39:89–93.